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Cinchonidine-induced restructuring of Pt/Al₂O₃ during enantioselective hydrogenation

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The intrinsic selectivity of cinchonidine-modified Pt/alumina is poor in the hydrogenation of 3,5-di(trifluoromethyl)-acetophenone but stirring of the catalyst system in toluene under nitrogen prior to reaction more than triples the ee. SEM and TEM analysis revealed dramatic restructuring of the catalyst and the Pt particles. We propose that the interaction of the hydroxy methyl-quinoline fragment (“anchoring moiety”) of cinchonidine with Pt is responsible for the restructuring. Reductive pretreatment at elevated temperature as well as the attrition induced by stirring in toluene accelerate the process. The higher ee is attributed to morphological changes of Pt, leading to the development of a more “selective” surface. The chirality of cinchonidine is unimportant in the restructuring and no correlation between the size of Pt particles and the ee has been found.

KEY WORDS: platinum/alumina; cinchonidine; catalyst restructuring; enantioselective hydrogenation; 3,5-di(trifluoromethyl)-acetophenone; quinoline.

1. Introduction

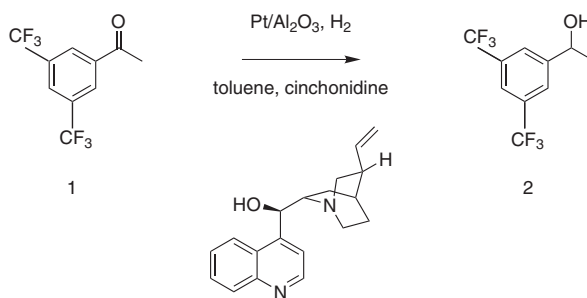
Since Orito's discovery in the late seventies [1,2], there has been a remarkable development in the understanding of the functioning of cinchona-modified Pt in the enantioselective hydrogenation of activated ketones [3–8]. The progress is less impressive when considering the critical role of the Pt surface in the enantioselection. The premature state in this area is illustrated by the contradictory opinions concerning the structure sensitivity of the reactions, i.e., the influence of metal particle size and shape on the enantioselectivity [9–11].

A closely related and thoroughly investigated observation is that pretreatment of Pt/alumina at elevated temperature in hydrogen can improve, sometimes even double, the enantiomeric excess (ee) in the hydrogenation of numerous activated ketones [2,9,12–19]. Recently, the enhanced enantioselectivity of Pt was attributed to an adsorbate-induced restructuring during the high-temperature treatment in hydrogen, whereas other effects, such as removal of surface impurities or change of Pt particle size, could be excluded [16].

Another effective preconditioning of supported Pt is the sonochemical activation under hydrogen, the procedure that increased the ee up to 98% in the hydrogenation of ethyl pyruvate [20]. The positive effect of ultrasonication, observed only in the presence of the cinchona alkaloid modifier, was attributed to a decrease of the metal particle size and to the evolution of a more

homogeneous metal particle-size distribution. An alternative explanation might be the removal of strongly adsorbed surface impurities [21]. However, applying a higher than optimal ultrasound frequency or too long a sonication time eliminated the selectivity improvement, even though the Pt particles were small and presumably cleaner. Hence, a direct correlation between the Pt particle size and ee is questionable; the shift in the particle-size distribution should rather be considered as an indication of restructuring and development of a more “selective” surface.

Here we report a new observation, the remarkable enhancement of ee during the hydrogenation of 3,5-di(trifluoromethyl)-acetophenone (**1**) with the Pt/alumina-cinchonidine (CD) system (scheme 1) [19]. It is even more intriguing that stirring of the catalyst slurry in the presence of CD before reaction more than tripled the initial ee, which is considered as the intrinsic enantioselectivity of the catalyst. In the light of a recent review



Scheme 1. Hydrogenation of 3,5-di(trifluoromethyl)-acetophenone (**1**) to 1-[3,5-di(trifluoromethyl)-phenyl]ethanol (**2**) over cinchona-modified Pt/Al₂O₃.

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Table 1
An overview on the various catalyst pretreatment methods

Method	Treatment in gas phase	Treatment in the liquid phase for 1 h in N ₂ (solvent composition)
(a)	No	No
(b)	Yes	No
(c)	Yes	No stirring (toluene, 1 , CD)
(d)	Yes	Stirring (toluene)
(e)	Yes	Stirring (toluene, 1)
(f)	Yes	Stirring (toluene, quinoline)
(g)	Yes	Tirring (toluene, CD)
(h)	Yes	Stirring (toluene, 1 , CD)

[22] and striking STEM evidence for adsorbate-induced chiral restructuring of a Cu(110) surface [23,24], the question arises whether CD would play a similar role in the restructuring of Pt/alumina.

2. Experimental

3,5-di-(trifluoromethyl)-acetophenone (**1**, ABCR), cinchonidine (Fluka) and quinoline (Fluka) were used as received.

Table 1 summarizes the conditions used in methods a–h to study the effect of catalyst pretreatments. For the gas-phase treatment (methods b–h), the 5 wt% Pt/Al₂O₃ catalyst (Engelhard 4759) was flushed with N₂ at 400 °C for 30 min in a fixed-bed reactor, followed by a reductive treatment in H₂ for 90 min at the same temperature. After cooling to room temperature in H₂, the catalyst was immediately transferred to the 50-mL glass reactor. In the subsequent pretreatments in the liquid phase (methods c–h), the catalyst was contacted with a toluenic solution under N₂ for 1 h, with or without stirring (500 rpm). After this treatment the missing components were added and the reaction was started by stirring at 500 rpm in hydrogen at 1 bar. In all the methods, 84 ± 2 mg catalyst, 3.68-mmol substrate, 13.6-μmol modifier and 10-mL solvent (toluene) were applied and the hydrogenation of **1** was followed for 2 h. The liquid-phase catalyst treatments and the hydrogenation reaction were carried out at 1 bar and room temperature (23–25 °C).

Control experiments using different amounts of catalyst and varying the stirring frequency did not indicate significant external mass transport limitation for the (slow) hydrogenation reactions. Intraparticle diffusion effects cannot be ruled out completely, but are unlikely due to the small catalyst particle size (< 100 μm).

Chemoselectivity, conversion and ee were determined by an HP 6890 gas chromatograph equipped with a chiral capillary column (WCOT fused silica 25 m × 0.25 mm, coating CP-Chirasil-Dex CB, Chrom-pack). Enantioselectivity is expressed as ee (%) = 100 × |(R–S)/(R + S).

The products were identified by GC/MS. Reproducibility of ee was within ±0.5%. A comparison of the optical rotation of the products (Perkin Elmer 241 Polarimeter) with literature data [25,26] revealed that in toluene the Pt-CD system afforded the (*S*)-enantiomer in excess. The actual or incremental ee is calculated as Δee (%) = (ee₁Y₁ – ee₂Y₂)/(Y₁ – Y₂), where Y represents the yield to the alcohol product (**2**) and index 2 refers to a sample taken subsequent to sample 1.

For transmission electron microscopy (TEM), the material was dispersed in ethanol and deposited onto a perforated carbon foil supported on a copper grid. The measurements were performed on a CM30 microscope (Philips; LaB6 cathode, operated at 300 kV). The high-resolution TEM (HRTEM) images were recorded with a slow-scan CCD camera. Volume-weighted mean particle size was calculated by the following formula [27]: $d_{av} = (\sum n_i d_i^3 / \sum n_i d_i^{2.19})^{1.23}$.

Scanning electron microscopy (SEM) was performed on a LEO 1530 Gemini, operated at 2 and 5 keV (field emission gun). The sample was deposited on silicon wafers and investigated as synthesized (uncoated).

3. Results and discussion

3.1. Catalytic experiments

The influence of various catalyst pretreatment methods on the hydrogenation of 3,5-di-(trifluoromethyl)-acetophenone (**1**) over CD-modified Pt/alumina is shown in figure 1. The conditions for the different pretreatment procedures are summarized in table 1.

When the catalyst was used as received, the initial ee was very low, 17% at 2 min, and increased slowly up to 22% in 2 h (figure 1, curve a). The incremental or differential ee in figure 2, curve a, shows that the actual ee at the end of the reaction was still below 25%.

After heat treatment of Pt/alumina in gaseous hydrogen, the initial ee was almost the same as without this treatment, but increased steadily up to 52% at 2-h reaction time (figure 1, curve b). Note that this is the standard pretreatment method of Pt/alumina that is used before the hydrogenation of **1** [19,28] and several other activated ketones. The incremental ee in figure 2,

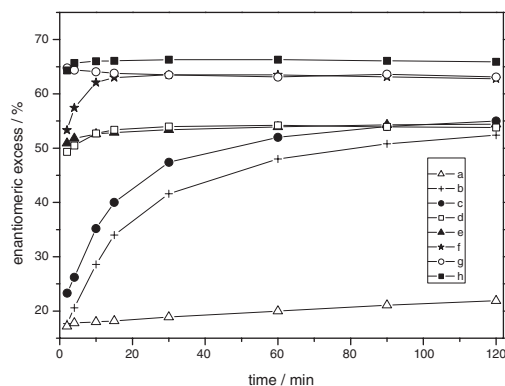


Figure 1. Time-dependent changes of enantioselectivity during hydrogenation of **1**. The letters a–h refer to the catalyst pretreatment methods summarized in table 1.

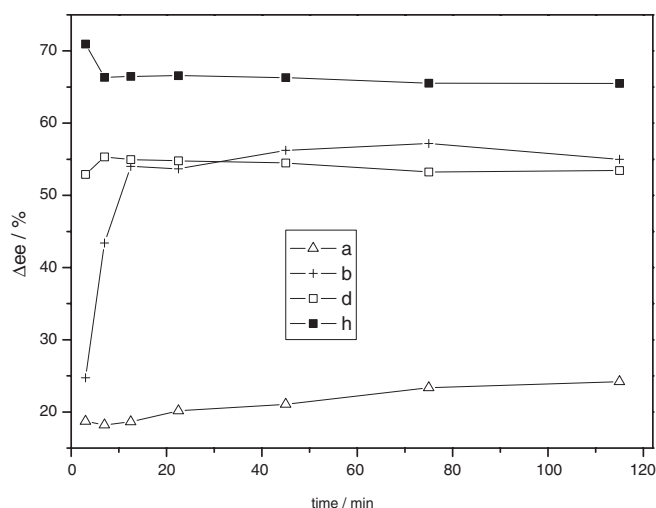


Figure 2. Time-dependent changes of incremental ee during hydrogenation of **1**. The letters a, b, d and h indicate the pretreatment methods, as shown in table 1.

curve b, shows that transformation of the catalyst during reaction is much faster after the reductive heat treatment and that after 10-min reaction time there is no significant change in the actual ee. Apparently, the heat treatment of Pt/alumina with gaseous hydrogen activates the catalyst for the subsequent development of more selective sites during the hydrogenation reaction.

Next, we tested various pretreatment methods (c–h) in the liquid phase to clarify the reason for the selectivity enhancement during reaction. All these treatments were carried out under nitrogen, subsequent to prereduction of the catalyst with gaseous hydrogen at 400 °C. During transfer of the prereduced catalyst to the reactor, the surface Pt atoms were oxidized by air. Note that the effect of various pretreatments on a reduced metal surface in hydrogen atmosphere would be distorted by hydrogenation of the modifier [21].

When the reaction mixture was left standing under nitrogen for 1 h before introducing hydrogen (figure 1,

curve c), the time dependence of ee remained similar, though the ee values were about 5% higher than those measured after the standard procedure (b). Repeating this pretreatment with stirring the reaction mixture under nitrogen (method h) afforded the highest ee. The incremental ee (figure 2, curve h) shows that the enantioselectivity was practically constant during this experiment. Obviously, stirring plays an important role in the evolution of more selective catalytic sites.

Next, before the hydrogenation of **1**, the catalyst was stirred in the presence of only toluene (d) or toluene and **1** (e), and the other reaction components were added before starting the hydrogenation reaction. Figure 1 shows that the enantioselectivities are almost identical and both curves d and e lie between b and h. We can conclude that (i) the reactant does not influence the transformation of the catalyst and (ii) not only the magnetic stirring but also the presence of CD are critical for achieving the highest ee. The same conclusions can be drawn from the comparison of curves g and h in figure 1 and the dependence of the incremental ee in figure 2, curves d and h.

Recent *in situ* ATR-IR studies [29,30] proved that CD adsorbs on Pt via its quinoline ring system, the so-called “anchoring moiety” of the modifier. Thus, we repeated the pretreatment by stirring the catalyst in toluene with quinoline (method f) instead of CD (method g). A comparison of the two curves f and g in figure 1 reveals that quinoline is almost as effective as CD in accelerating the restructuring of Pt. The small difference is likely due to the presence of the OH group in CD, whose function is also involved in the adsorption of CD when it is present in the so-called “open-3” conformation [31].

In some experiments, the time of catalyst pretreatment in the toluenic solution was varied. When applying method d, i.e., stirring in toluene only, a decrease of the pretreatment time diminished the positive effect on the enantioselectivity. For example, stirring of the slurry only for 5 min instead of 1 h decreased the initial ee from 49 to 26%. In contrast, when stirring of the catalyst in toluene in the presence of **1** and CD (method h), 5 min was sufficient to achieve the same ee as that measured after 1 h. This observation corroborates the accelerating effect of CD on the catalyst restructuring.

Figure 3 shows some examples of the time dependence of the conversion of **1**. After catalyst pretreatments b, d and h, the reaction rate decreased slowly with time, as expected. In contrast, when the catalyst was used as received (curve a), an unusual rate enhancement was observed after about 30 min. This behavior may be attributed to the slow removal of some strongly adsorbed impurity from the Pt surface, from which species are removed by the reductive treatment at elevated temperature when applying methods b–h.

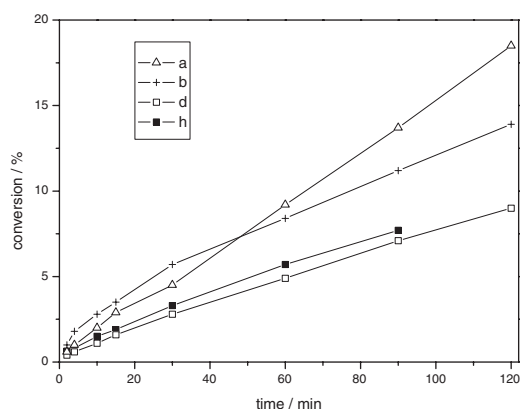


Figure 3. Conversion of **1** as a function of time after the catalyst pretreatment methods a, b, d and h (for details, see table 1).

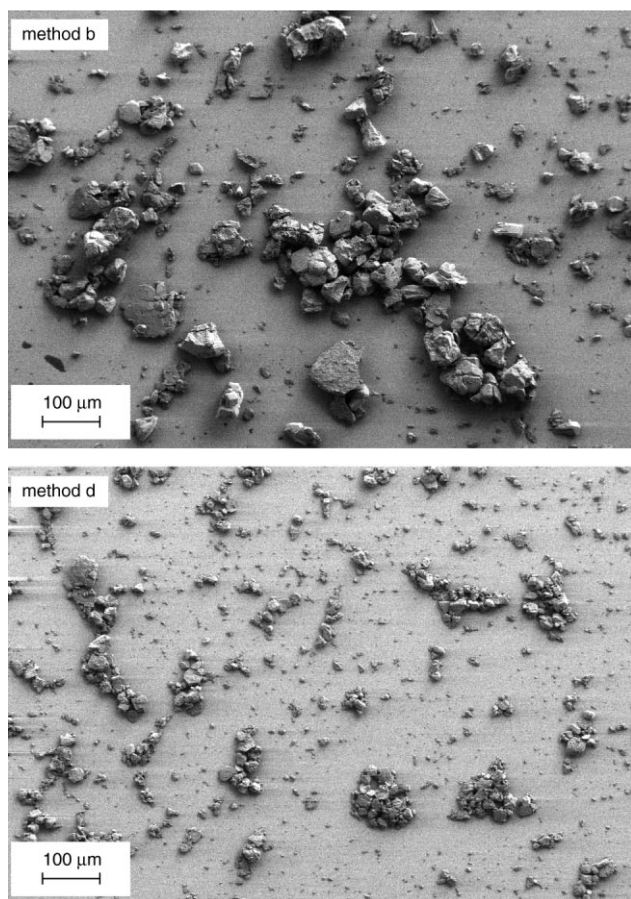


Figure 4. Secondary electron SEM images after reductive treatment of Pt/alumina in hydrogen at 400 °C (method b), and after the subsequent stirring of the catalyst in toluene for 1 h (method d). For details of the pretreatment methods see table 1.

3.2. Electron microscopy: evidence for catalyst restructuring

Electron microscopy provided a strong proof for the restructuring of Pt/alumina during the various catalyst treatments prior to the enantioselective hydrogenation of **1**. The scanning electron micrographs (SEM) in figure 4 show that the catalyst particles are considerably

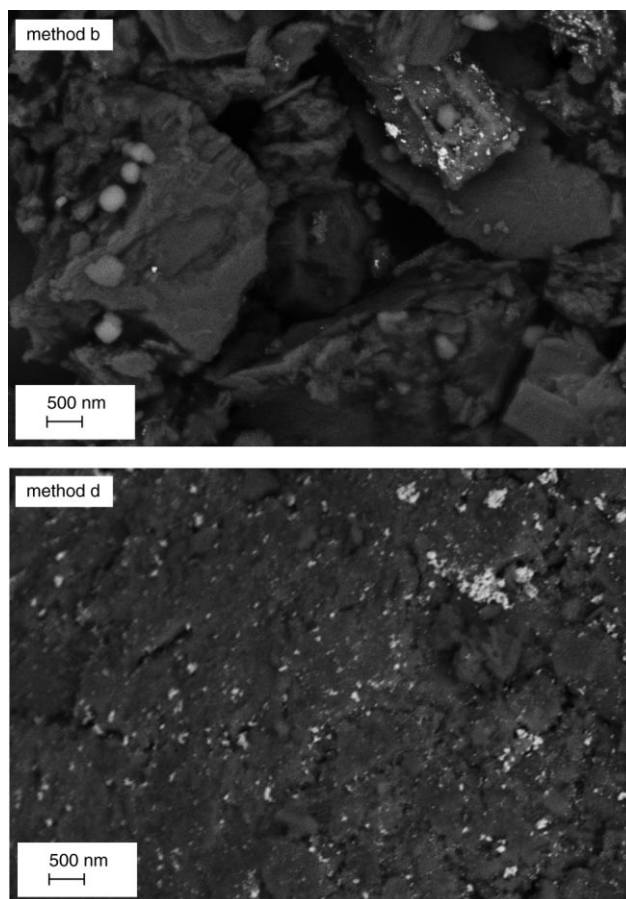


Figure 5. Back-scattered electron SEM images after reductive treatment of Pt/alumina in hydrogen at 400 °C (method b), and after the subsequent stirring of the catalyst in toluene for 1 h (method d). The white spots are Pt particles. Details of the pretreatment methods are listed in table 1.

smaller after stirring in toluene for 1 h (method d) than before this treatment (method b). It has been shown earlier for the same type of catalyst by light scattering that the mean catalyst particle size decreased to one-half in about 8 min because of magnetic stirring of the catalyst slurry [32].

The back-scattered electron SEM pictures indicate redistribution of the Pt particles during the liquid-phase treatment (figure 5). Stirring of the catalyst in toluene for 1 h (method d) resulted in a relatively even distribution of small Pt particles (white spots) from the unevenly distributed bigger Pt particles developed during the reductive treatment at 400 °C (method b).

The effect of catalyst pretreatments on the Pt particle-size distribution was studied by high-resolution transmission electron microscopy. The untreated catalyst ("as received") contained small, well-dispersed Pt particles (method a, figure 6). The reductive treatment at 400 °C (method b, figure 7) broadened the Pt particle-size distribution and almost doubled the mean particle size. The subsequent stirring of the catalyst in toluene for 1 h (method d, figure 8) decreased the metal particles again and narrowed the particle-size distribution. This

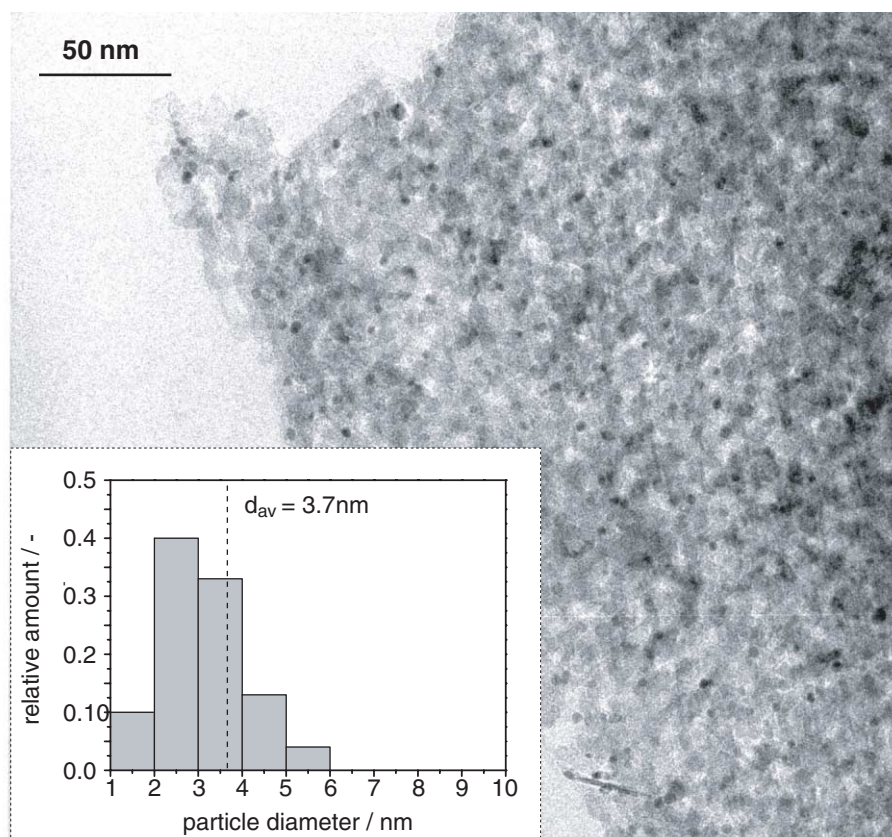


Figure 6. TEM image and metal particle-size distribution of Pt/alumina after pretreatment a (see table 1). The black spots are Pt particles.

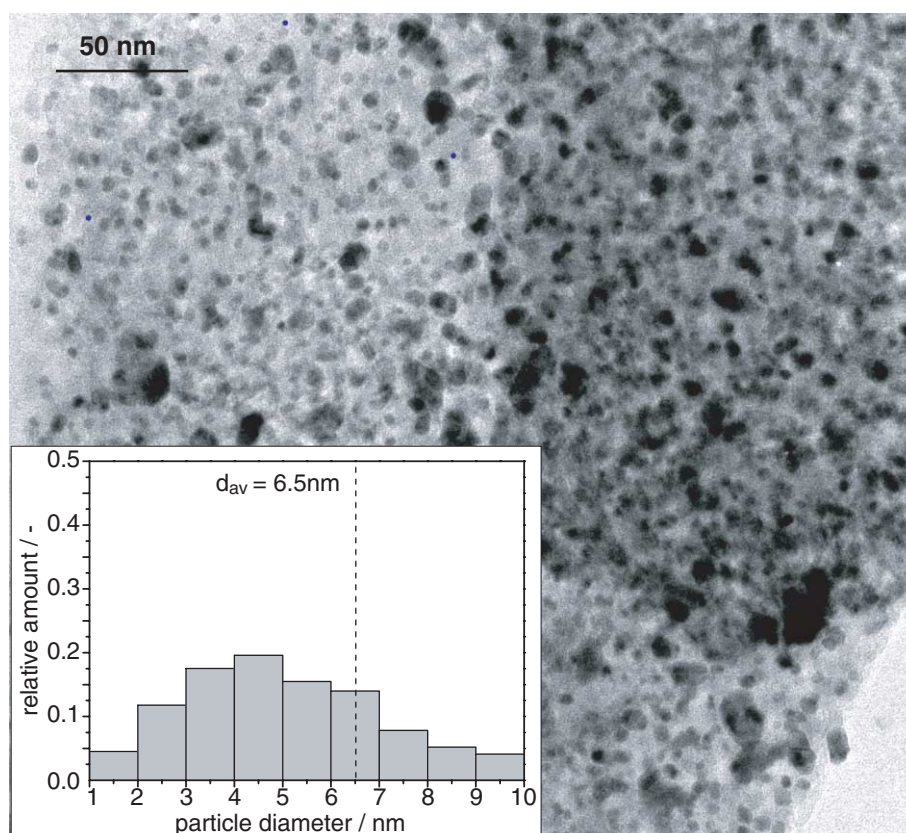


Figure 7. TEM image and metal particle-size distribution of Pt/alumina after pretreatment b (see table 1). The black spots are Pt particles.

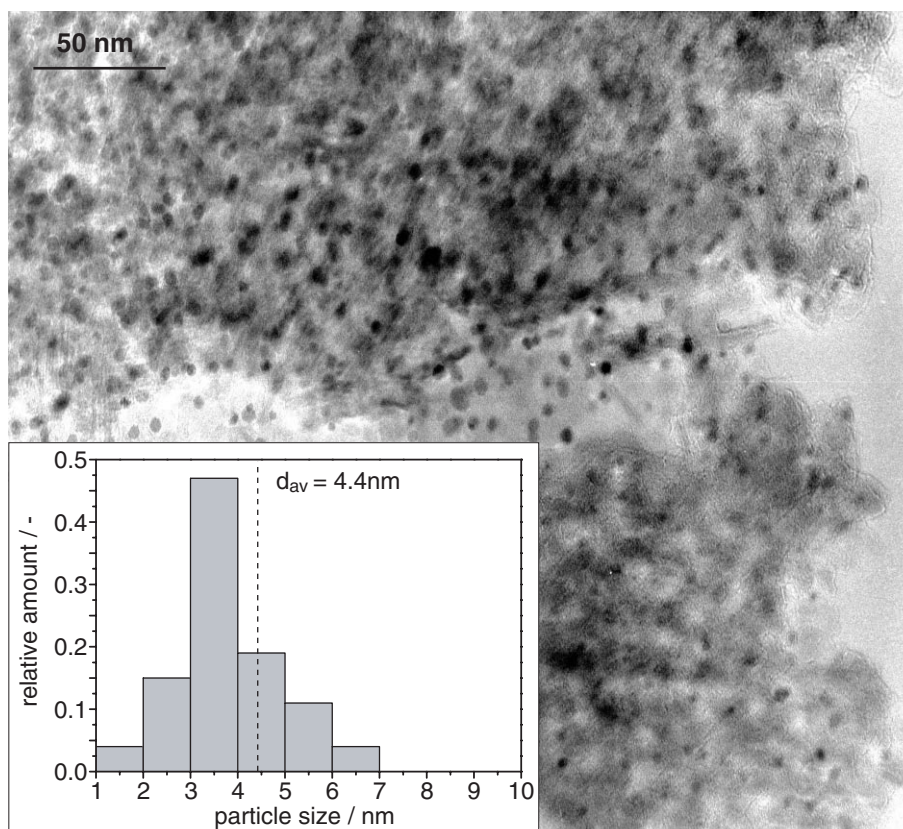


Figure 8. TEM image and metal particle-size distribution of Pt/alumina after pretreatment d (see table 1). The black spots are Pt particles.

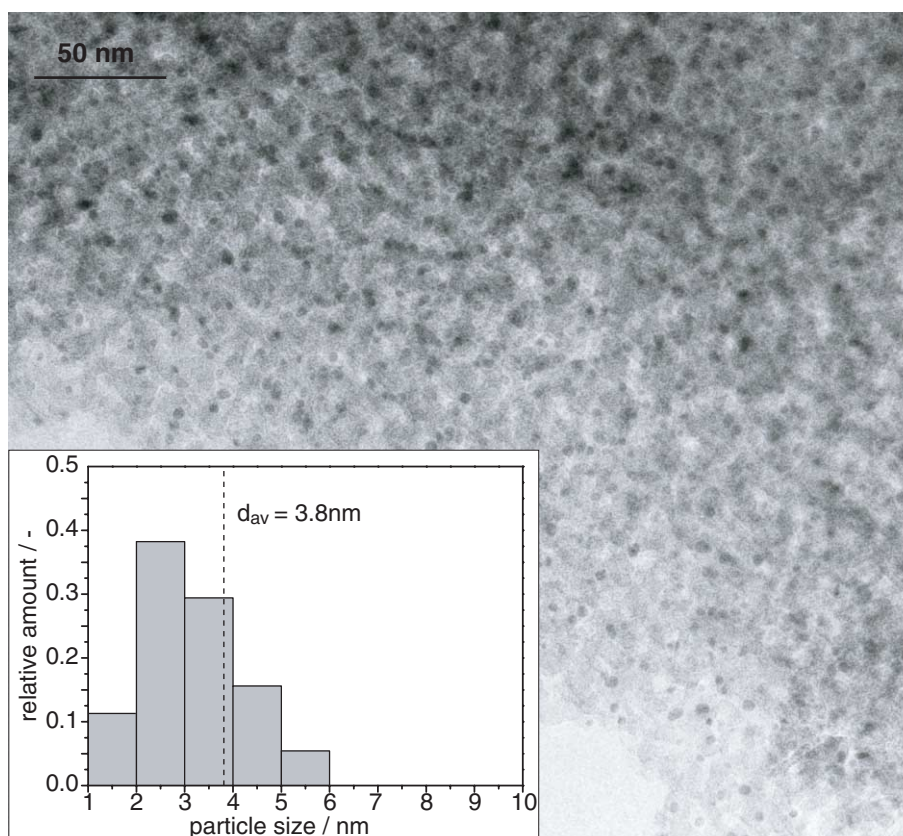


Figure 9. TEM image and metal particle-size distribution of Pt/alumina after pretreatment h (see table 1). The black spots are Pt particles.

redistribution was more pronounced when CD was present in toluene during stirring (method h, figure 9). Astonishingly, the particle-size distribution in the least selective, untreated catalyst and in the most selective catalyst preconditioned according to method h are almost identical (cf. figures 6 and 9). Clearly, no correlation between the Pt particle size and the enantioselectivity can be drawn, though the changes presented in figures 6–9 confirm the importance of structural transformation during catalyst pretreatment.

We have to emphasize that electron microscopy is yet the only method that supports the catalyst restructuring. ICP-AES analysis of the reaction solution did not indicate any dissolved platinum species.

3.3. “Chiral” restructuring?

It has been speculated for long that the enantioselectivity of chirally modified metals might be due to chiral restructuring of the metal surface induced by the strongly adsorbed modifier (for a recent review see [22]). The striking effect of CD on the restructuring of Pt/alumina, as shown in figure 1, apparently supports this assumption. However, the control experiment with quinoline revealed that not the chiral structure but presumably only the hydroxymethyl-quinoline fragment of CD is crucial for the restructuring. We propose that the strong interaction of this moiety with Pt plays an important role in the morphological changes observed.

There exists substantial literature on the adsorbate-induced restructuring of metal surfaces [33,34]. A closely related phenomenon is the remarkable change of the structure and selectivity of Pd during the Rosenmund reaction, where structural transformation is accelerated by the catalyst modifier quinoline [35]. During the morphological changes, larger Pd particles and thin single-crystal plates with stepped and kinked sites were formed.

4. Conclusions

The most important observations of the present study can be summarized as follows:

1. During the slow hydrogenation of 3,5-di-(trifluoromethyl)-acetophenone (**1**), the enantioselectivity increases remarkably because of the morphological restructuring of the Pt/alumina catalyst, which presumably involves surface restructuring of the Pt particles.

2. A key parameter for the catalyst restructuring is the presence of cinchonidine (CD) during preconditioning in toluene under nitrogen. Without the chiral modifier, the transformation of the catalyst to a more selective material is slow and incomplete.

3. Pretreatment in hydrogen at elevated temperature activates the catalyst for the subsequent restructuring in

the liquid phase; the latter is accelerated by magnetic stirring of the reaction mixture.

We assume that the strong adsorption of the hydroxymethyl-quinoline fragment of CD is responsible for the “reshaping” of the Pt particles. In other words, the chirality of the modifier is unimportant for the structural changes. It is not clear yet, which types of active sites are required for higher enantioselectivity. Considering the relatively large number of Pt sites occupied by the CD-**1** transition complex, identification of the “selective” and “nonselective” ensembles of surface sites seems to be a demanding task for future research.

An important consequence of the present observations is that due care is required for the interpretation of kinetic data in heterogeneous enantioselective catalysis. Catalyst restructuring should always be considered as a possible distorting factor.

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